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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,033	08/01/2001	Rosanne M. Crooke	ISPH-0592	5785
20995 7590 01/12/2007 KNOBBE MARTENS OLSON & BEAR LLP 2040 MAIN STREET FOURTEENTH FLOOR IRVINE, CA 92614			EXAMINER EPPS FORD, JANET L	
			ART UNIT 1633	PAPER NUMBER

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	01/12/2007	ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 01/12/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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eOAPilot@kmob.com

<p align="center"><b>Office Action Summary</b></p>	<p><b>Application No.</b></p> <p>09/920,033</p>	<p><b>Applicant(s)</b></p> <p>CROOKE ET AL.</p>	
	<p><b>Examiner</b></p> <p>Janet L. Epps-Ford</p>	<p><b>Art Unit</b></p> <p>1633</p>	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 10-26-06.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,8-10,12,13,15-20,28-30 and 33-36 is/are pending in the application.
- 4a) Of the above claim(s) 15-19 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,8-10,12,13,20,28-30 and 33-36 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>11-13-06</u> + 8-25-06 | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Claims 1, 8-10, 12-13, 20, 28-30 and 33-36 are presently pending for examination. Claims 15-19 are withdrawn.

#### ***Claim Rejections - 35 USC § 102***

3. The rejection of claims 1, 4-5, 8-13, 20, 28, 29-34, and 36-38 under 35 U.S.C. 102(a or e) as being anticipated by Bennett et al. (US Patent No. 6172216, Published January 9, 2001), is withdrawn in response to Applicant's amendment to the claims.
4. The rejection of claims 1, 4-5, 8-13, 20, 28, 29, 31, 33-34, and 36-38 under 35 U.S.C. 102(b) as being anticipated by Baker et al. (WO 00/00504 A1), is withdrawn in response to Applicant's amendment to the claims.

#### ***Claim Rejections - 35 USC § 103***

5. The rejection of claims 1, 4-5, 8-13, 20, 28, 29-39 under 35 U.S.C. 103(a) as being unpatentable over Bennett et al. as applied above, in view of Wengel et al. (US 2002/0068708A1), is withdrawn in response to Applicant's amendment to the claims.
6. Claims 1, 8-10, 12-13, 20, 28-30 and 33-36 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Rouy et al. (US Patent No. 6,512,161; or WO 99/35241 A1; see IDS of 4-07-06; citations given for US Patent), and Eggerman et al. (See IDS of 4-06-05) in view of GenBank Accession No NM\_000384 (Huang et al. Reference #1), Monia et al. (US 5,656,612; see Reference A of PTO-892 mailed

1/14/2003), Agrawal et al. (2000, see Reference U of PTO-892 mailed 1-13-2004), and Wengel et al. (US 2002/0068708A1), for the reasons of record.

Applicant's arguments filed 10-26-06 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that they have identified several oligonucleotides that have unexpected properties...however it is noted that SEQ ID NO: 3 is 14,121 base pairs in length. The instant claims are drawn to antisense compounds that are 20 base pairs in length, therefore the scope of the instant claims encompasses a total of potentially 706 non-overlapping antisense compounds which scan the length of SEQ ID NO: 3, and an exponential number of potentially overlapping antisense compounds that would scan the full length of SEQ ID NO: 3. Due to variability in the functional activity of antisense compounds targeting distinct regions of SEQ ID NO: 3, as evidenced by Applicant's own Table 1, wherein antisense oligonucleotides targeting SEQ ID NO: 3 vary in their ability to inhibit the expression of apolipoprotein B mRNA expression, Applicant's "several oligonucleotides that have unexpected properties" are not representative of the full scope of antisense compounds encompassed by the claims.

Moreover, Applicants argue that the cited references do not show a single oligonucleotide compound targeted to a nucleic acid encoding apolipoprotein B that can produce at least 70% inhibition of apolipoprotein B at a concentration of 150 nM. Contrary to Applicant's assertions, and absent evidence to the contrary, the teachings of Eggerman et al. (Federal Register, June 7, 2000, Vol. 65, no. 110, pages 36150-36151)

teach antisense targeting apolipoprotein B, having the ability to decreased apoB mRNA expression in human liver cell lines by up to 80%.

As stated in the prior Office action, it would have been obvious to one of ordinary skill in the art, at the time of the instant invention, to modify the teachings of Rouy et al. and Eggerman et al. with the teachings of GenBank Accession No. NM\_000384, Monia et al., Agrawal et al., and Wengel et al. to design non-catalytic oligonucleotides compounds of 12 to 30 nucleobases in length, that specifically hybridizes to the nucleotide sequence set forth in SEQ ID NO:3, excluding the start codon region, and further modifying the oligonucleotides with one or more sugar modifications, internucleoside linkage modifications, and nucleobase modifications.

One of ordinary skill in the art would have been motivated to design compounds of 12 to 30 nucleobases in length since Rouy et al. expressly teaches antisense oligonucleotides targeting apolipoprotein B mRNA comprising at least 20 nucleobases in length. Moreover, one of ordinary skill in the art would have been motivated to design oligonucleotide compounds targeting apolipoprotein B mRNA comprising one or more sugar modifications, phosphorothioate modified internucleoside linkages, and 5'-methylcytosine modified nucleobases, since Monia et al. teaches that these modifications are known to both increase hybridization efficiency and nuclease resistance of oligonucleotide compounds comprising these modifications. Moreover, Monia et al. teach that oligonucleotides comprising these modifications possess a high target site specificity and increased cellular uptake in comparison to unmodified antisense oligonucleotides. Furthermore, one of ordinary skill in the art at the time of

the instant invention would have been motivated to make this modification since the prior art teaches that antisense compounds comprising LNA modifications produces antisense compounds with stability towards exonucleolytic degradation, effective delivery into cells, and display unprecedented binding affinity to both RNA and DNA (see Wengel et al., page 3, lines 25-35).

Additionally, one of ordinary skill in the art seeking to further understand the role of apolipoprotein B gene expression in cellular processes, would have been motivated to design antisense oligonucleotides targeting the mRNA encoding the apolipoprotein B gene as defined by SEQ ID NO: 3 of the instant specification, since GenBank Accession No. NM\_000384 clearly set forth the nucleotide sequence of SEQ ID NO: 3 as the sequence encoding the full-length apolipoprotein B mRNA. Moreover, NM\_000384 clearly defines the 5'-UTR as occurring before nucleotide 129, start codon region as beginning at nucleotide 129, and the coding sequence as extending from nucleotide 129 to nucleotide 13820, therefore the 3' UTR would be defined as the remaining sequence corresponding to nucleotides 13821 through 14121. Moreover, according to Agrawal et al., if the nucleotide sequence of a gene was known, designing antisense oligonucleotides to target the various regions of that gene, including the 5' UTR, the coding sequence and the 3' UTR (see above description of Agrawal et al.) that would allow the ordinary skilled artisan to further elucidate the role of that gene of interest in various cellular processes.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections

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are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Moreover, as per MPEP § 716.01(c)[R-2], "It is well settled that unexpected results must be established by factual evidence." The arguments of counsel cannot take the place of evidence in the record.

It remains, therefore, that the claims remain rejected for the reasons of record.

### ***Conclusion***

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

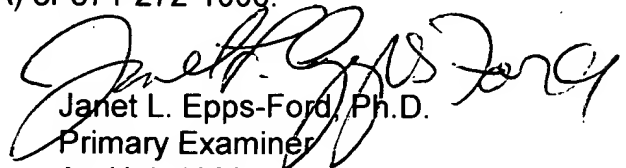
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

  
Janet L. Epps-Ford, Ph.D.  
Primary Examiner  
Art Unit 1633

JLE